REMARKS

Reconsideration of the application is respectfully requested. Claims 2-5 and 10-30 are pending in this application. In the Office Action, the Examiner has incorrectly indicated that only claims 2-5 and 10-16 are pending. Claims 15-30 were added in the Response to Office Action filed February 16, 2005. Applicants therefore request that the Examiner consider the merits of all the pending claims, including claims 17-30.

The following remarks apply to all of the pending claims.

Rejections Under 35 U.S.C. § 102(b)

Claims 2-5, 10, 15, and 16 have been rejected under 35 U.S.C. § 102(b) as anticipated by Boegesoe et al. (U.S. Patent No. 4,943,590). Boegesoe is cited by the Examiner as disclosing escitalopram in the claimed dosages.

The rejection is respectfully traversed, and reconsideration is requested.

All of the pending claims (including claims 2-5, 10, 15, and 16) are directed to methods of treating panic attacks comprising administration of escitalopram. However, as the Examiner acknowledges, Boegesoe does not disclose the treatment of panic attacks. Office Action at p. 4. Therefore, claims 2-5, 10, 15, and 16 are not anticipated by Boegesoe. *See* MPEP § 2131 (for a reference to be anticipatory, it must teach each and every limitation of the claim); Merck *& Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1372 (Fed. Cir. 2003) (method claim not anticipated because the reference failed to teach the claimed therapeutic use). Accordingly, applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 2-5 and 10-16 have been rejected under 35 U.S.C. §103(a) as obvious over Boegesoe in view of Bouwer et al., *J. Affective Disorders* 49 (1998) 79-82. Boegesoe is cited by the Examiner as disclosing administration of escitalopram in the claimed dosages. The Examiner cites Bouwer as teaching administration of citalopram to treat social phobia. According to the Examiner, citalopram is "structurally and functionally identical to escitalopram" and "[s]ocial phobia is a form of panic attack." Office Action at pp. 4-5. From this, the Examiner concludes that it would have been obvious for one of ordinary skill to treat panic attacks by administering escitalopram.

The rejection is respectfully traversed, and reconsideration is requested.

First, applicants wish to clarify that citalopram is not "structurally ... identical" to escitalopram. Rather, citalopram is a racemic compound comprising S- and R- enantiomers; and escitalopram is the S-enantiomer. Thus, escitalopram has a distinct structure. Further, citalopram is not "functionally identical" to escitalopram because the citalopram enantiomers have been found to exhibit different activities. Moreover, it is surprising and unexpected that escitalopram has a significantly greater potency than racemic citalopram for treating panic attacks. This is discussed in an article entitled "R-Citalopram Attenuates Anixolytic Effects of Escitalopram in a Rat Ultrasonic Vocalisation Model," which was recently published in the *European Journal of Pharmacology* by co-inventor Connie Sánchez (*Eur. J. Pharm.*, 464:155-158 (2003); previously submitted as Exhibit C with Response to Office Action filed November 21, 2003). In the study reported in this article, co-inventor Sánchez surprisingly found that the R-enantiomer of citalopram ("R-citalopram"), when combined with escitalopram, inhibits the anti-anxiety (including anti-panic) activity of escitalopram.

The anxiolytic activity of escitalopram and R-citalopram was determined by footshock-induced ultrasonic vocalization in rats. Each group of rats was administered (i) a vehicle, (ii) escitalopram alone or in combination with R-citalopram, (iii) racemic citalopram, or (iv) R-citalopram alone. The rats were also tested at normal and enhanced levels of 5-hydroxytryptamine (5-HT).

The results for citalopram and escitalopram in normal rats and rats with enhanced levels of 5-HT are shown in Table 1 on page 156 of the article, which is reproduced below:

Table 1

Administration (min before shock regimen)	Drug (30 min), s.c.		Drug (50 min) + 1-5HTP (25 mg/kg, 20 min), s.c.	
	ED_{50} (mg/kg)	Max inhibition (%)	ED_{50} (mg/kg)	Max inhibition (%)
Citalopram	ND[a]	64	1.1 0.69 - 1.8	100
Escitalopram	0.51 0.34 - 0.77	97	0.052 0.033 - 0.082	100

Four 1.0 mA inescapable footshocks, each of 10 s duration and with 5 s intershock intervals were applied. One min after the last shock the accumulated time spent emitting ultrasounds was measured during a 5 min period. Results are expressed as ED_{50} values with 95% confidence intervals and % maximum inhibition. ND = not determined, a: biphasic response with maximum inhibition at 0.50 mg/kg.

In normal rats, citalopram only partially inhibited ultrasonic vocalization (64% inhibition), while escitalopram nearly completely inhibited the response (97% inhibition). *See* Table 1 column entitled "Drug (30 min), s.c." When the basal levels of 5-HT in rats were increased by administering L-5-HTP (25 mg/kg), the median effective dose (ED_{50}) of citalopram was twice as much as that needed to obtain maximum inhibition in a normal rat. In contrast, the median effective dose of escitalopram in rats having enhanced levels of 5-HT was one-tenth

(1/10) that needed to obtain maximum inhibition in a normal rat. In other words, escitalopram exhibits greater potency in rats with increased 5-HT levels than in rats at normal 5-HT levels, while citalopram exhibits decreased potency. Furthermore, escitalopram was about 20-times more potent than citalopram in the rats with enhanced 5-HT basal levels.

The ability of R-citalopram to attenuate (or reduce) the therapeutic effect of escitalopram was tested further by comparing the footshock-induced ultrasonic vocalisation in rats dosed with escitalopram alone and those dosed with escitalopram (0.24 mg/kg) and R-citalopram (0.48 mg/kg) concomitantly. Based on the test results shown in the insert of Figure 1 on page 156, Sánchez concluded that "[t]he addition of R-citalopram significantly attenuated the inhibitory effect of escitalopram on footshock-induced ultrasonic vocalization." *See* p. 157, left column, last full paragraph.

These results demonstrate that R-citalopram attenuates the anxiolytic effect of escitalopram in footshock-induced ultrasonic vocalisation. This is especially surprising because "it would be expected that R-citalopram's histamine H1 receptor antagonistic activity would enhance rather than attenuate the effect of escitalopram on foot-shock-induced ultrasonic vocalisation." *See* p. 157, right column, last sentence of the second full paragraph, reproduced in full below (italics added):

> Of the 144 targets tested in *in vitro* binding affinity studies ..., the only site for which citalopram and R-citalopram, but not escitalopram, showed appreciable affinity was that of the histamine H1 receptor. *In vitro* studies in isolated guinea pig ileum show that R-citalopram is a weak histamine H1 receptor antagonist (unpublished observation). Histamine H1 receptors are involved in mediation of ultrasonic vocalization and the histamine H1 receptor antagonist, mepyramine, antagonizes footshock-induced ultrasonic vocalization .... Thus, it would be expected that R-citalopram's histamine H1 receptor antagonistic activity would enhance rather than attenuate the effect of escitalopram on footshock-induced ultrasonic vocalization.

Therefore, the significantly greater potency of escitalopram compared to racemic citalopram for treating panic attacks is surprising and unexpected. For the foregoing reasons, Boegesoe and Bouwer, alone or in combination, fail to render obvious the presently claimed invention. Accordingly, applicants respectfully request that this rejection be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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